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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FALK, ANNE MARIE	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/930,781	WU ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed March 24, 2004 (hereinafter referred to as "the response") has been entered. Claim 1 has been amended.

Claims 1-5 remain pending in the instant application.

The rejection of Claim 1 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,034,297 (Vierling) is withdrawn in view of the amendment to the claims which now recite the new limitation "wherein the mammal has a normal immune system."

At page 6 of the response, Applicants object to the Examiner's interpretation of the claim language because the term "tolerant" is being given its usual and ordinary definition rather than the very narrow meaning that Applicants prefer. Applicants argue that they are permitted to be their own lexicographer. This is true, as long as the special definition applied is not repugnant to the art. See MPEP §608.01(o). The MPEP explicitly states that no term may be given a meaning repugnant to the usual meaning of the term. In the instant case, the very narrow meaning for the term "tolerant" is repugnant to the meaning given in the art. The references already cited in this case provide ample support for the Examiner's position. For example, at paragraph [0043], Brown et al. state that "immunotolerance can be induced in the host animal. This can either be a general immunosuppression or a specific suppression of an immune reaction to particular epitopes." Furthermore, Rhim et al. (1995) refer to athymic nude mice as "immunotolerant" (see abstract; p. 4942, column 2, paragraph 2; and p. 4945, column 1, paragraph 3). Furthermore, general immunosuppression caused by immunosuppressive drugs induces host "tolerance" as describe by Kuby (1997) who states that "[i]mmunosuppressive drugs act not only by blocking T-cell activation but also by inducing host tolerance to the allogeneic cells" (p. 566,

column 2, paragraph 2). A textbook definition of "tolerance" is simply a "state of immunologic unresponsiveness" (see Kuby, p. 608).

Thus, the Examiner maintains that, although the specification states that the term "tolerant" does not refer to a state of general immunosuppression, but rather indicates a state of antigen-induced non-responsiveness of lymphocytes achieved by clonal deletion, cell-mediated suppression, or anergy directed specifically toward the introduced human cells (page 18, paragraph 0062 of specification), one of skill in the art would understand the term "tolerant" to encompass general immunosuppression. The more narrow interpretation suggested in the specification is not the conventional understanding in the art. Furthermore, the claims do not refer to specific immunosuppression. Thus, where the claims recite the term "tolerant, the term is construed to broadly encompass general immunosuppression as well as specific immunosuppression, unless further limitations narrow the scope of the claim.

The rejection of Claim 1 under 35 U.S.C. 103(a) as being unpatentable over Rhim et al. (1995) in view of U.S. Patent No. 6,034,297 (Vierling) is withdrawn in view of the amendment to the claims.

The rejection of Claim 1 under 35 U.S.C. 103(a) as being unpatentable over WO 96/39810 (Knudsen, 1996) in view of U.S. Patent No. 6,034,297 (Vierling) is withdrawn in view of the amendment to the claims.

Terminal Disclaimer

The terminal disclaimer filed on March 24, 2004 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 6,525,242 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: the claims now recite a mammal that has a "normal immune system." The specification does not use this terminology, but rather uses the terminology referred to below in the "new matter" rejection. MPEP § 608.01(o) states that "[t]he use of a confusing variety of terms for the same thing should not be permitted."

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants have not pointed to any support in the specification as-filed for the new limitation "wherein the mammal has a normal immune system." The new limitation constitutes new matter because the specification does not specifically contemplate using a mammal that has a "normal immune system." At page 7, paragraph [0021], the specification refers to a first embodiment of the method comprising inducing tolerance in an **immunocompetent** host non-human animal. The specification also uses the term "intact," but does not use the term "normal immune system." At page 7, paragraph [0023], the specification states "[i]mmunocompetent chimeric animals of the invention exhibit the further advantage

of having an immune system which is intact but for exhibiting tolerance toward the human cells comprised in the animal's liver."

This is a new matter rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5 stand rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent Application No. 2001/0007153 A1 (filed June 16, 1997; Brown et al.).

Brown et al. discloses a non-human animal model having incorporated therein a solid chimeric organ in a manner such that the animal, previously incapable of supporting a viral or pathogenic infection, becomes susceptible to infection. The reference teaches that it is particularly desirable to make animals that support a Hepatitis C infection (see paragraph 0038). The reference specifically teaches that, in the absence of stimulation, intrasplenic injection of hepatocytes can create a chimeric liver with approximately 1% of the hepatocytes derived from an allogeneic or xenogeneic donor (paragraph 0039, referring to Ledley et al.). The reference further teaches that a higher representation of donor cells may be achieved by administration of compounds that are hepatotoxic, such as D-galactosamine, carbon tetrachloride, and pyrrolizidine alkaloids (paragraph 0039). The reference teaches inducing immunotolerance by specific suppression of an immune reaction (paragraphs 0043 and 0044). The reference specifically points out that the same allogeneic or xenogeneic source used for the implantation

can be used as a source for the tolerization as well and that, although intact hepatocytes are needed for the implantation, lysates of cells have been found to be as effective as whole cells for induction of tolerance (paragraph 0044). The reference specifically teaches using the HuH-7 cell line (paragraph 0092)

Thus, the claimed invention is disclosed in the prior art.

At page 4 of the response, Applicants argue that the disclosure of Brown et al. is not enabling because the invention is not described in sufficient detail. Applicants state that Brown's disclosure appears to be no more than a mere wish or plan for obtaining the claimed invention. Applicants assert that the superficial disclosure of non-immunocompromised animal models in Brown would not enable one of ordinary skill in the art to practice the instantly claimed invention. At page 5 of the response, Applicants point out that Brown practices only immunodeficient animal models referring to RAG-2 mice in Example 1, and Applicants assert that Brown's immunodeficient animals were much more laborious to create than it would have been to follow their own disclosure regarding non-immunocompromised animals. Applicants conclude that this indicates that the disclosure was not enabling even for its author.

The Examiner does not agree. RAG-2-deficient mice have been available commercially for many years. Brown did not labor over creating them, they purchased them from Taconic Farms (see paragraph 0092). Furthermore, Brown need not disclose what is already known in the art. Brown discloses that tolerance to a specific set of antigens can be achieved through neonatal tolerance, thymic tolerance, T cell depletion or inactivation, and oral tolerization (see paragraph [0044]). Methods for neonatal tolerization, thymic tolerization, and oral tolerization were already known in the art in 1997. See, for example, Ilan et al. (J. Clin. Invest. 99: 1098-1106, March 1997) which describes successful oral tolerization to adenoviral antigens, Ilan et al. (J. Clin. Invest. 98: 2640-2647, 1996) which describes tolerization by injection of soluble antigen into the functional thymus, Nussenblatt et al. (J. Immunol. 144: 1689-1695, 1990) which describes oral tolerization to S-antigen, Kline et al. (Annals of Thoracic Surgery 57: 72-75) which describes *in utero* tolerization of rat fetuses, and Walter et al. (PNAS 93: 3056-3061, 1996) which

describes neonatal tolerization. At paragraph [0044], Brown refers to U.S. patent application serial number 08/808,629 as describing means of carrying out various methods of tolerization. PCT/US98/03606 is a continuation of 08/808,629 and WO 98/37917 is the PCT publication having the same disclosure. However, the prior application is not relied upon for enabling disclosure. Since the prior art clearly disclosed numerous means for inducing specific tolerance, the disclosure of Brown need not provide a repetition of these various protocols, and one of skill in the art could, armed with the disclosure of Brown and the prior art available at the time, using nothing more than routine experimentation, carry out the methods disclosed by Brown and thereby produce immunocompetent mammals comprising human-mammal chimeric livers. Thus, the disclosure of Brown is considered enabling.

Reduction to practice is not required for anticipation. Case law establishes that anticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure. *In re Donohue*, 766 F.2d 531, 533 [226 USPQ 619] (Fed. Cir. 1985). A reference may enable one of skill in the art to make and use a compound even if the author or inventor did not actually make or reduce to practice that subject matter. *Bristol-Myers*, 246 F.3d at 1379; see also *In re Donohue*, 766 F.2d at 533.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing

date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571) 272-0804. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Dianiece Jacobs, whose telephone number is (571) 272-0532.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER